

Application No.: 09/421,971

Attorney Docket No.: SALK2350

Filing Date: October 20, 1999

(088802-5351)

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**REMARKS**

Courtesies extended to Applicants' representative during the telephone interview held March 24, 2005, are acknowledged with appreciation.

In accordance with the present invention, there are provided chimeric proteins comprising a covalent fusion of at least two functional protein units, wherein each functional protein unit comprises a ligand binding domain, an optional hinge domain, a DNA binding domain, and a dimerization domain of a member of the well-known and thoroughly characterized steroid/thyroid hormone nuclear receptor superfamily (see Figure A schematic below).

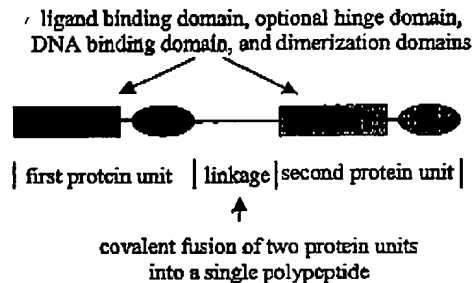


Figure A – exemplary chimeric fusion protein construct

As discussed during the telephone interview, the present claims, as amended herein, are directed to a chimeric protein comprising at least two functional protein units, wherein each of these functional protein units is further required to be one of a defined group of members of the steroid/thyroid hormone nuclear receptor superfamily. The functional protein units form a functional entity, such that the resultant chimeric protein is biologically active.

By the present communication, claims 1, 5-11, and 13-14 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims.

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It is respectfully submitted that entry of the amendments submitted herewith is proper because these amendments place the present application in condition for allowance or at a minimum, in better condition for appeal. It is further submitted that these amendments merely implement the alternative claim language discussed during the telephone interview with the Examiner. Accordingly, entry of the amendments submitted herewith is respectfully requested.

Upon entry of the proposed amendments submitted herewith, claims 1, 2, 5-11, and 13-22 will be pending. The present status of all claims in the application is provided in the Listing of Claims presented herein beginning on page 2 of this communication.

**The Rejection under 35 U.S.C. § 112, First Paragraph—Enablement**

The rejection of claims 1-2, 5-11 and 13-22 under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to reasonably provide enablement for the chimeric proteins as claimed, is respectfully traversed for at least the reasons already of record.

In particular, it is respectfully submitted that the present claims are fully enabled by the specification. Indeed, as acknowledged by the Examiner, "the specification . . . is enabling for a chimeric protein comprising a fusion of EcR-USP/RXR into a functional dimer" (see page 2 of the Office Action). Applicants respectfully disagree, however, with the Examiner's assertion that the specification allegedly "does not reasonably provide enablement for chimeric proteins comprising two functional protein units wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily" (see page 2 of the Office Action). Contrary to the Examiner's assertion, it is respectfully submitted that the application meets the standard for enablement of the present invention.

Moreover, as discussed during the telephone interview, the claims, as amended herein are directed to chimeric proteins comprising at least two functional protein units, each of which is further required to be one of a defined group of members of the steroid/thyroid hormone nuclear receptor superfamily, and therefore, are submitted to be fully enabled.

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Furthermore, the conclusion by the Examiner that the specified claims allegedly fail to comply with the enablement requirement is based on an erroneous and incomplete evaluation of the Wands factors, as follows.

**1) The nature of the invention**

The present invention is drawn to chimeric proteins comprising a covalent fusion of at least two functional protein units, wherein each functional protein unit comprises a ligand binding domain, an optional hinge domain, a DNA binding domain, and a dimerization domain of a defined group of members of the well-known and thoroughly characterized steroid/thyroid hormone nuclear receptor superfamily.

**2) The state of the prior art**

The state of the prior art with respect to members of the steroid/thyroid hormone nuclear receptor superfamily is quite advanced, as evidenced by the extensive reference cited by the Examiner, Aranda and Pascual, *Physiol. Rev.* 81:1269-1304, 2001 (hereinafter referred to as "Aranda"). As previously noted, this reference is fully consistent with Applicants' assertion that the specification in fact supports enablement of the full scope of the present claims.

In efforts to support this rejection, the Examiner's discussion of Aranda (see, for example, page 3, lines 8-17 of the Office Action) focuses on the differences between members of the steroid/thyroid hormone nuclear receptor superfamily, asserting that the Aranda reference "teaches that the superfamily is subdivided into six distinct subfamilies" (see page 3, lines 12-13 of the Office Action). However, the fact remains that amongst members of this superfamily, there are far more similarities than differences, even between superfamily members from different "subfamilies," as defined by Aranda. That's why they are all considered to be part of a single superfamily.

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Moreover, as discussed during the telephone interview, the claims as amended herein are directed specifically to receptors from a single subfamily of receptors, i.e., "Class I," as defined by Aranda (see Table 1 at page 1272 of Aranda).

**3) The relative skill of those in the art**

The relevant level of skill in the art is high.

**4) The predictability or unpredictability of the art**

It is respectfully submitted, in view of the high level of skill in the art and the abundance of information regarding steroid/thyroid hormone nuclear receptors available to those of skill in the art, that the making of the chimeric proteins as contemplated by the present claims is reasonably predictable.

However, in order to reduce the issues and expedite prosecution, the claims as amended recite a discrete group of members of the steroid/thyroid hormone receptor superfamily, all of which are categorized in the Aranda reference as the so-called "Class I" receptors.

**5) The breadth of the claims**

The Examiner's assertion that "the breadth of the claims encompass a large number of possible proteins" (see page 4, line 13 of the Office Action) is irrelevant. The number of species embraced by the claims is irrelevant. What is important is whether undue experimentation would be required of one of skill in the art to identify other chimeric proteins embraced by the claims. It is respectfully submitted that undue experimentation would not be required under the present circumstances.

Contrary to the Examiner's assertion, the present claims are submitted to be of proper scope, especially as amended herein. Given the highly related nature of all members of the steroid/thyroid hormone nuclear receptor superfamily, a showing with respect to one member of the superfamily can readily be extended to other members of the superfamily.

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However, in order to reduce the issues and expedite prosecution, the chimeric proteins of claim 1, as amended herein, are defined as comprising functional protein units selected from a defined group of members of this superfamily. Specifically, claim 1 requires that at least one functional protein unit is selected from the retinoid X receptor or its insect homolog, ultraspiracle protein and the other functional protein unit is selected from a defined group of superfamily members, all of which are defined by Aranda as "Class I" receptors (see Table 1 at page 1272 of Aranda).

**6) The amount of direction and guidance presented**

It is respectfully submitted that Applicants have provided more than a reasonable amount of guidance with respect to any experimentation required to carry out the present invention. With respect to the functional protein units, the specification teaches domains that can be used to form each functional protein unit and presents exemplary domains for use in the practice of the invention, as described previously. One of skill in the art, in light of the teachings of the specification and knowledge in the art, could readily determine appropriate domains to assemble in the construction of a chimeric protein in order to achieve one or more biological functions. Moreover, Example 1 teaches the complete design and construction of exemplary chimeric fusion constructs.

**7) The presence or absence of working examples**

It is respectfully submitted that the working examples employ receptor members that are highly representative of the entire superfamily. Thus, additional examples with further superfamily members are clearly not necessary. Indeed, given the well characterized nature of all members of the nuclear receptor superfamily, additional examples with further superfamily members would merely be superfluous. Therefore, the claims should not be limited to just the working examples provided.

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**8) The quantity of experimentation necessary**

Applicants respectfully disagree with the Examiner's assertion that "[i]t would require undue experimentation for one of skill in the art to make and use the claimed polypeptides." (See page 4, lines 7-8 of the Office Action). The Examiner's concern with the quantity of experimentation required to practice the present invention is respectfully submitted to be misplaced as the quantity of experimentation is only one factor involved in determining whether undue experimentation is required; moreover, time and difficulty of experiments are not determinative if they are merely routine (MPEP § 2164.06).

It is respectfully submitted that the amount of direction or guidance provided by the present specification is commensurate in scope with the claims, as amended.

Therefore, the experimentation required would not be undue, "since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation would proceed" (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Clearly, Applicants have provided substantial guidance on how to proceed with experimentation, as well as routine procedures and programs to do so.

However, consistent with the telephone discussion with the Examiner, and in order to reduce the issues and expedite prosecution, the claims, as amended herein, are directed to chimeric proteins comprising functional protein units selected from a discrete group of well-defined members of the steroid/thyroid hormone receptor superfamily. Such chimeric proteins clearly meet the standard for enablement of the present invention. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

**The Rejection under 35 U.S.C. § 112, First Paragraph—Written Description**

The rejection of claims 1-2, 5-11 and 13-22 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as

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to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, is respectfully traversed for at least the reasons already of record.

Specifically, Applicants respectfully disagree with the Examiner's assertion that "[n]o common structural attributes identify the members of the genus." (See page 6, lines 8-9 of the Office Action). Indeed, contrary to the Examiner's assertion, this superfamily contains a remarkably uniform domain structure that was well-known in the art at the time of filing of the present application.

Applicants further disagree with the Examiner's assertion that "[t]here is no description of the conserved regions which are critical to the structure and function of the genus claimed." (See page 6, lines 21-22 of the Office Action). Since the steroid/thyroid hormone nuclear receptor superfamily is well-defined, including the ligand binding domain, optional hinge domain, DNA binding domain, and dimerization domains thereof, there is no merit to the Examiner's above-quoted concern. Moreover, Applicants are not merely relying on that which is known in the art, in addition, the specification includes extensive discussion with respect to domains that can be used to form each functional protein unit and presents exemplary domains for use in the practice of the invention.

Finally, Applicants further disagree with the Examiner's assertion that "while the claims are drawn to a protein, there is no structure (i.e. sequence) set forth for the protein, only a function is set forth" (see page 7, lines 20-21 of the Office Action). Contrary to the Examiner's assertion, the present claims require proteins having the structure of at least two defined members of the steroid/thyroid hormone nuclear receptor superfamily. Moreover, it is respectfully submitted that presentation of sequences is not necessary because the chimeric proteins embraced by the present claims comprise functional protein units whose sequences are well-known and readily available to those of skill in the art. Indeed, presentation of the sequences encoding the claimed chimeric proteins would needlessly clutter the application with

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that which is known to those of skill in the art. Therefore, one of skill in the art would have no reason to doubt that Applicants were in possession of the present invention at the time of filing.

However, consistent with the telephone discussion with the Examiner, and in order to reduce the issues and expedite prosecution, the claims, as amended herein, are directed to chimeric proteins comprising functional protein units selected from a discrete group of well-defined members of the steroid/thyroid hormone receptor superfamily. Such chimeric proteins are fully supported by the specification especially in view of that which was known in the art at the time of filing. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

#### Rejections under 35 U.S.C. § 102(b)

With respect to the rejection of claims 1, 14, 19, 20, and 22 under 35 U.S.C. § 102(b) as allegedly being anticipated by Lees et al. (Mol Cell Biol 10(10):5529-31, 1990) as evidenced by Peters et al. (Mol Endocrinol 13(2):286-96, 1999) referred to on page 2 of the Office Action, it is presumed that this rejection has been withdrawn because no further reference to this rejection is made in the remainder of the Office Action. If this presumption is incorrect, clarification is respectfully requested.

The rejection of claims 1-2, 14, and 22 under 35 U.S.C. § 102(b) as allegedly being anticipated by Hutchens et al. (Mol Endocrinol 4(2):255-67, 1990), is respectfully traversed.

Applicants' invention, as defined, for example, by amended claim 1, distinguishes over Hutchens et al. at least by requiring a chimeric protein comprising:

a fusion of at least two functional protein units...

wherein at least one functional protein unit is selected from the group consisting of the retinoid X receptor and the *ultraspiracle* protein;

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wherein the other functional protein unit is selected from the group consisting of retinoid X receptor, ecdysone receptors, Vitamin D3 receptors, retinoic acid receptors, peroxisome proliferator-activated receptors, thyroid hormone receptors, steroid and xenobiotic receptors, farnesoid X receptors, and liver X receptors...


Hutchens does not disclose or suggest any such chimeric proteins. Instead, Hutchens is directed to formation of stable homodimers of estrogen receptors (a Class III receptor, as opposed to the Class I receptors embraced by the present claims; see Table 1, page 1272 of Aranda). Accordingly, reconsideration and withdrawal of this rejection of claims 1-2, 14, and 22 under 35 U.S.C. § 102(b), are respectfully requested.

#### Conclusion

In view of the above amendments and remarks, prompt and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: April 8, 2005



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